

## CURRENT METHODS IN THE TREATMENT OF TUBERCULOSIS\*

### *The Second Harlow Brooks Lecture*

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THE general improvement in the picture of tuberculosis in many countries in which facilities and trained personnel are available to cope with it may be interpreted, at least in part, as evidence of the greater efficacy of treatment. In the United States the lowering of the death rate from this disease to a level of 12.6 per 100,000 in 1953, which represents about 6 per cent of the rate prevailing in 1900 and a drop of 22 per cent in one year, certainly indicates the increasing success of measures for control. Among these a direct reflection of the better results of treatment is the declining death rate in tuberculosis hospitals and sanatoria. For many years and as late as the 1940s this averaged close to 20 per cent of all patients departing from these institutions each year;<sup>1</sup> in 1953, in New York tuberculosis hospitals, it was 7 per cent. However, 29 per cent of the patients departing from these hospitals in 1953 left against medical advice, compared with 20 per cent in 1950.<sup>2</sup> In many cases this is a consequence of the early and marked symptomatic improvement under chemotherapy which often deceives patients into thinking wrongly that the disease is healed. On the debit side, it must also be recognized that in this and other countries the tuberculosis death rate has decreased relatively little among elderly men, a relatively high rate still prevails among the non-white members of our population, the registration of new cases has not declined greatly, and the chance of recovery is materially less for a patient of small means than it is for his economically prosperous brother.<sup>3</sup> Tuberculosis continues throughout the world to be a major threat to health and life. It is clear, therefore, that therapy is just one means of attack and that its success, aside from its own intrinsic merits, depends also on many related factors.

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The approach to treatment is directed by three major considerations: The biological characteristics of the tubercle bacillus, particularly its great faculty of long survival in the tissues of the body, the unique form and composition of the lesions which it causes, and the natural resistance of the host. As to the bacillus, there is abundant evidence that during the development of lesions there is a great proliferation of the microbes while others die and undergo lysis. Under natural conditions of healing, particularly after fibrosis and calcification are well developed, some lesions become sterile but this usually seems to require a number of years; in others the bacillus survives and remains capable of causing relapses after several decades. Under the influence of chemotherapy with various combinations of streptomycin, isoniazid and para-aminosalicylic acid, administered for a period of months, there is clear-cut evidence not only of inhibition or suppression of bacterial proliferation but also, in many lesions, of profound modification of the biological properties of *some* of the bacilli so that they are no longer capable of growing on the usual artificial culture media or of causing progressive disease in guinea pigs. It has also been found, among bacilli obtained from patients treated with isoniazid, that such attenuation of virulence occurs as the bacilli first manifest resistance against the further action of the drug. These phenomena suggest that some of the bacilli may be killed rather rapidly by the treatment, but the question is still debatable and under investigation.<sup>4,6</sup> There are curious discrepancies since some patients, who yield these attenuated strains from their sputum, have been observed to continue suffering from progressive tuberculosis and later to die from it; furthermore, it has been found that some of these bacterial strains which fail to grow on ordinary media may be induced to do so by specialized techniques<sup>7</sup> and some which are relatively harmless in guinea pigs may kill mice.<sup>6</sup> The observations have stimulated new studies of bacterial metabolism and may well lead to identification of the mechanisms by which the specific drugs act. In view of the unsettled state of our knowledge and considering the frequency of failures of treatment and of relapses of the disease after the temporary success of treatment, we are obliged at present to work on the assumption that tubercle bacilli do survive in the lesions of patients, even after a few years of uninterrupted chemotherapy, and that some of these organisms retain their virulence. A more sanguine view may become justified as new drugs and new regimens are tested and become available. The demonstration by Mc-

Dermott and his associates<sup>8</sup> that combinations of pyrazinamide and isoniazid may sterilize the tissues of tuberculous mice, if not those of human patients, gives reason for interest in this direction and possibly for hope. Unless and until a sterilizing therapy for human tuberculosis is discovered, treatment can be considered fully effective only when it leads to the establishment of conditions in the body by which surviving bacilli will be confined and thereby rendered innocuous for the remainder of the patient's life.

Aside from the durability of the bacillus living in an unfavorable environment, the character of the lesion which it produces, most often in the lungs, adds to the difficulties of therapy. Were this a simple inflammation like pneumococcal pneumonia, it might be expected to resolve completely, leaving no trace, but the pathological hindrance in tuberculosis is the invariable necrosis of tissue whenever the disease is of sufficient extent to cause illness. This familiar caseation has many implications. It is responsible through the processes of liquefaction and sloughing for spreading the infection by various channels. Examples are the contamination of the blood stream by the ulceration of such a lesion into a pulmonary vein and, much more often, the discharge of infectious pus into the bronchial tree and its connections, resulting in progressive involvement of the lungs, the larynx, the intestine, and other structures along the way. The cavity left in the lung is usually an omen of chronic disability and eventually of a fatal outcome unless it can be dealt with effectively by the various means of treatment. Likewise the partially healed solid necrotic focus, more or less encapsulated by fibrous tissue, becomes a refuge in which living tubercle bacilli may lurk for indefinite periods of time. Sometimes, because of an identifiable accident, but more often for reasons unknown, softening and liquefaction of the necrotic focus is resumed and the progeny of these organisms may emerge to initiate the relapse which is the familiar characteristic of the disease. Under prolonged chemotherapy, it has been demonstrated that the physical character of the lesion has much influence on the behavior of the tubercle bacilli; drug resistance becomes manifest earlier among those recovered from actively excavating lesions than it does among those from solid and almost encapsulated caseous lesions. The local biochemical factors which may influence these differences have been studied and discussed by Dubos<sup>9</sup> and his associates. Coping with the cavitory case remains the most difficult problem of treatment. Under the influence of

specific drugs, the walls of the cavity may be so transformed by fibrosis that the tuberculous elements are difficult to demonstrate; a cyst-like cavity is left and this is sometimes called "open healing." Tubercle bacilli often disappear from the sputum. This is a unique effect of chemotherapy, but not to be relied upon as permanent since the later relapse rate in these cases is high and diligent histological searches of the walls of resected cavities usually reveal at least small remnants of tuberculous tissue. Early symptomatic recovery under treatment is much to be desired but it is also obviously important to judge the implications of the remaining lesions and to extend treatment for their permanent control or eradication, if possible.

Probably no available treatment of tuberculosis would be efficacious were it not for the natural resistance of the human body against the infection. The nature of resistance is poorly understood and we have no accurate means of measuring it; its adequacy is judged best after the event, rather than before it. Despite this, it is the major defense on which every patient must rely to recover from tuberculosis and to remain well. Resistance seems to fluctuate, sometimes rapidly; it declines during sustained periods of excessive physical or emotional stress and rises when all is serene and restful; hence the basis of rest treatment. Among the many factors which influence resistance a few may be identified statistically in groups of the population, such as age, sex, and occupational conditions, and others suggest themselves in the individual case, such as associated diabetes and malnutrition.

Of all the tangible factors which determine the outcome of a case, the most important are the stage and clinical character of the disease at the time of diagnosis and the promptness with which treatment is instituted. Far advanced bilateral pulmonary tuberculosis always has had a dismal prognosis under any form of treatment, and long survival is exceptional. Today, the possibility of symptomatic benefit is much better and life may be greatly prolonged in many cases. At the other extreme, early pulmonary tuberculosis, if diagnosed while its extent is still limited to small areas, usually responds well to rest treatment alone indicating the relative adequacy of natural resistance. However, in some of these cases relapses and deaths do occur, particularly if the disease is not arrested within two years after its inception.<sup>10</sup> With chemotherapy, rest treatment, and surgical resection of the lesion in refractory cases a permanent recovery rate close to 100 per cent probably can be anticipated.

Methods of treatment are various, offering the possibility of many choices according to the needs of the individual patient. The use of rest to enhance natural resistance and to exert certain favorable mechanical influences on the local lesion is indispensable during the early months. With the use of chemotherapy and surgery, the duration of disability is materially abbreviated in many advanced cases, but there is still a considerable relapse rate which compels many of these patients to resume resting. In the early minimal case, however, the prospect of permanent recovery is so good that a long initial period of rest and graduated activity amounting to one to two years, is usually advisable before full time work is resumed. The optimum degree of rest and the means of obtaining it varies according to the circumstances; confinement to bed does not always mean absolute rest. The objective, of course, is maximum relaxation and relief of tension since this has been shown empirically to favor the best response. How this is to be achieved is a matter of judgment and trial in each case.

With the exception of apparently stable and healed lesions the specific drugs are now employed in virtually all cases of tuberculosis. The choice of drugs and regimens and the duration of administration is determined individually; it is desirable to continue until the signs of local healing give reasonable assurance that future exacerbations will not occur. Judgment is very difficult, particularly with respect to future potentialities of arrested lesions, and in many instances the adequacy of treatment can be determined only by a period of close observation and follow-up.

Surgical methods for the control or elimination of severe disease have been perfected to a remarkable degree and are employed in many carefully selected cases. The favorable results of these operations depend greatly on the preparation of the patient, usually by a lengthy period of treatment and the recognition of the time when conditions are optimum for avoiding operative and postoperative risks. Surgical measures to control pulmonary disease by collapsing the lung, such as the classical thoracoplasty or some modification of it, are effective in two-thirds to three-quarters of patients selected for such procedures,<sup>11,12</sup> and these figures probably will be improved when, in addition to rest, chemotherapy is also used. Collapsing the lung by artificial pneumothorax, which checked the disease in many cases,<sup>13</sup> is employed much less often since chemotherapy became available, largely because of the necessarily

long duration of the treatment and the incidence of pleural complications. Simultaneously, there has been an upward surge in many institutions of the use of pneumoperitoneum, although few depend on this alone and many are skeptical of its value except in some bilateral cavitory cases.

Of the many drugs which exert an inhibitory action against the proliferation of tubercle bacilli, those which have had the most thorough testing are streptomycin (and dihydrostreptomycin), isoniazid, and para-aminosalicylic acid. The sulfones and amithiozone also have been well studied but because of their limited effectiveness are not widely used. Pyrazinamide is effective in human subjects for at least short periods of time, particularly when administered with other drugs, and may well prove in the future to be a valuable agent; it may cause toxic hepatitis. Viomycin possesses the virtue of exerting active bacteriostasis when administered to patients whose tubercle bacilli are found to be resistant against other drugs, such as streptomycin. However, viomycin often causes toxic effects, particularly on the eighth cranial nerve, which necessitates great caution in its administration.<sup>14</sup> Other drugs which seem to hold promise are also under investigation. Principally because of the necessity of lengthy periods of treatment and the obstacle of drug resistance which usually becomes manifest within relatively short periods of time (two to twelve weeks) after a single drug is administered daily, it becomes necessary to devise means of delaying such manifestations, and this is accomplished in part by the administration of two or more drugs simultaneously.

The rationale of treatment of tuberculosis depends greatly on an understanding of its evolution, its behavior in particular sites, and the various mechanisms of healing. The most complex and difficult problems are encountered in disease of parenchymal organs, such as the lungs and the kidneys. In the lungs, the early lesion is exudative and pneumonic and this type of reaction is a constant component of all acute and extensive lesions and, in more or less mild degree, also of many chronic lesions. In early and acute pulmonary disease, even before symptoms become severe, there are important potentialities either of rapid and marked resolution of inflammatory exudate or of necrosis not only of the exudate which has been poured into the alveolar spaces but also of the pulmonary tissue itself. Necrosis and excavation in acute cases may occur extensively within several weeks or months, while in more chronic

cases the process may be very slow and in time may come to a halt. Destroyed tissue is never restored to normal and at best can only be replaced by fibrous organization. The importance of this in the acute case is so vital that one may digress to point at the grievous error of treating early tuberculous pneumonia with penicillin on the mistaken assumption that the cause is the pneumococcus. The loss of even several weeks of time in instituting proper therapy may spell the difference between extensive resolution and extensive destruction with all the implications of each. The immediate problem in any case of active disease is to favor suppression of the infection as promptly as possible and it is at this point that chemotherapy exerts its greatest effects. The rate of its action varies according to the severity of the case. In symptomatic acute disease of several weeks duration prompt critical lowering of the fever often occurs, and this may be accompanied by a rather dramatic improvement of the general condition including a gain in weight. Simultaneously, the output of sputum may be rapidly reduced and in several weeks or months may be inconsequential. This, together with the disappearance of tubercle bacilli from the sputum or gastric washings, reflects the local effects of bacteriostasis, namely, a diminution or cessation of exudation through and from the wall of cavities. Its importance is self-evident when it is recalled that continuing purulent bacillary discharges from cavities are responsible so often for the spread of the disease. Accompanying such effects there is almost always a rather rapid resolution of surrounding exudate which has not yet undergone necrosis and frequently a diminution of the size of cavities. In very acute caseous pneumonia in which the resistance of the patient inferentially is assumed to be relatively low, the response to chemotherapy and bed rest often is much slower. High fever may not abate for six or eight weeks and the diminution of other symptoms is also very gradual. In still other cases of very extensive bilateral disease with severe symptoms, the effects of the best available treatment are unavailing and the patient may die in a few weeks or several months. In more chronic cases with mild symptoms the response to chemotherapy is more consistently favorable, but, because of areas of necrosis and fibrosis the anatomical regressions, best demonstrated by roentgenograms, are usually less striking.

In any event, after symptomatic control has been achieved and maximum regression of the lesions has occurred, the problem of assessing and

interpreting the implications of residual lesions remains. These may be represented by rather clean fibroid cavities which are dried out, more or less inspissated solid caseous lesions which may be enclosed in some fibrosis, and small foci which may be almost completely transformed into fibrous tissue. The last are likely to remain healed but, as stated, the other two have a great tendency later to flare up into renewed activity causing further extension of the disease and clinical relapse. Such residues, if not very large, may slowly regress under further rest treatment and chemotherapy continued in some cases for another one or two years. Finally, small cavities may be completely obliterated and all fibrocaseous lesions may seem to be well circumscribed and arrested. Under favorable conditions of living, the prognosis for permanent recovery is good but because of viable bacilli contained in the lesions, vigilance must be exercised throughout the patient's life to detect the slightest evidence of recurrence. Larger lesions of a cavitory or solid fibrocaseous composition are looked upon with apprehension even though symptomatic recovery may have been complete. The solid lesion may remain quiescent indefinitely but its tendency, even after a lapse of a few years, to undergo liquefaction, sloughing and discharge of infection into the bronchial tree is well recognized. The threat is greatest when the lesion is known to have sloughed previously, when it is more than one or two centimeters in diameter, when its origin is relatively recent and when it occurs in young people. Because of the multiplicity of factors involved, the outcome cannot be predicted with certainty. Chemotherapy and some form of general treatment may be continued pending observation but the finding of tubercle bacilli by cultures of the sputum or gastric contents after a year or more of such treatment is a sign of imperfect healing and a liability of the lesion to progress again. Then one may be so convinced of the threat that surgery may be decided upon for removal of the focus.

It has not been shown that collapse of the lung by thoracoplasty or artificial pneumothorax materially influences the future of these solid caseous lesions. If surgical treatment is indicated, therefore, resection is favored. The time may be appropriate after symptoms have been relieved and the lesion has become stabilized, isolated and well circumscribed; depending on its original appearance, this may require six months or more. Notable success has been achieved by skilled surgeons in removing these lesions by resection of lobes, segments or sub-segments, thus conserving healthy or less involved tissue. There is a risk of complications



such as pleural fistula and tuberculous empyema and the incidence of these varies according to the selection of cases and other circumstances.

In the case of persisting pulmonary cavity the prospect of relapse on discontinuing chemotherapy or because of the development of drug resistance is very great and it becomes necessary, if possible, to deal with the case surgically. Collapse of the diseased part by thoracoplasty or some similar procedure may be possible if the anatomical relations are suitable; healing may be adequate and permanent after these relatively clean fibrotic cavity walls are collapsed and brought together. This may be the procedure of choice when the disease has been extensive and residual fibrocaseous lesions are widely distributed, but if the severely destructive disease has been confined to one lobe it is preferable, after due preparation by rest and chemotherapy, to resect the lobe totally, and this may be followed by partial thoracoplasty to reduce the vacant space.

Bilateral resectional surgery is occasionally carried out, particularly for the removal of localized lesions which threaten to be sources of future relapses but the range of its usefulness is narrow.

Owing to the unfortunate fact that most cases of pulmonary tuberculosis on first diagnosis are moderately advanced or far advanced, the immediate results of treatment in many are little more than palliative. Extensive acute bilateral tuberculous pneumonia which ordinarily would run its fatal course within a few months may be arrested and the patient's life may be prolonged, but the disease is not improved beyond the point of chronicity. These cases, together with chronic bilateral cavitory disease which is so frequently encountered at the time of diagnosis, present most difficult problems. With initial chemotherapy and rest treatment the symptomatic recovery may be striking but the future course is likely to be precarious. The extent of destruction of tissue may be so great and widely distributed that surgery has no place. It has been proposed in these cases that chemotherapy might be continued with some effect throughout the remainder of the patient's life. It is known that some of these patients may live for several decades, provided they accept what is virtually a life of chronic invalidism. With chemotherapy such a state may be more bearable since symptoms may be more or less controlled, but in many cases the prospect is faced that progressive fibrosis will encroach upon respiratory function, producing strain of the right heart and rather miserable disability from this cause; furthermore,

while in some cases chemotherapy may be continued with effect for four or five years, it must be recognized that no combination of drugs has been proved to be effective indefinitely. Many of these patients will join the army of chronics which is considered to be the main source of infection in the community. The possibility has been recognized and cases have been documented in which a primary infection has been found due to drug resistant strains of tubercle bacilli presumably acquired from such previously treated patients. Thus it is seen the complexity of the problem increases. The obvious solution is to apply the known and effective means of diagnosis and treatment before the disease has advanced to a vast and irreparable extent.

The nature of tuberculosis of the kidney is analogous in some respects to that of the lung, especially in not causing symptoms until necrosis and sloughing have occurred. Chemotherapy may be prompt and impressive in its immediate effects and, depending somewhat on the severity of the tissue destruction, the urine may be sterilized within a few weeks or months. But here, as in the lung and other parenchymal structures, the necrotic and excavating lesion may continue harboring viable organisms which may lead to exacerbations even after a long period of quiescence. It is recognized, therefore, that symptomatic improvement is only one criterion, that prognosis hinges largely on the extent of tissue destruction, and that in many cases nephrectomy or partial nephrectomy may be necessary to assure the best results.<sup>15</sup> With prolonged chemotherapy for advanced bilateral cases, symptomatic relief may continue for some years but the ultimate duration and degree of this remains to be determined.

The influence of the different structures and relations of tuberculous tissues is further exemplified by the behavior of the disease in the mucous and serous membranes. Under natural conditions the lesions have a much greater tendency to heal themselves than those, for instance, in the lung or kidney, and this difference is even more striking under the influence of chemotherapy. Lesions in the mucosa of the larynx, intestine and bladder recede rapidly and are soon covered by a regrowth of the epithelium. Symptoms often subside with remarkable rapidity. The explanation relates largely to the fact that such lesions, when they have gone on to ulceration, cast off their necrotic elements readily and rapidly, leaving only shallow defects. Repair is not hindered by the presence of large necrotic elements and proceeds rapidly and effectively.

In acute generalized miliary tuberculosis which, because of the overwhelming infection, usually runs its fatal course within three or four months the possibilities of recovery under chemotherapy are favorable if the diagnosis is made early and treatment is initiated promptly. The progress of the myriad tiny lesions is arrested and most or all of them eventually may be converted to fibrous tissue. It is conceivable that many of these minute lesions may actually be sterilized; in contrast the same amount of tuberculous tissue concentrated into one or several massive and confluent pulmonary lesions could not be expected to respond so favorably. Relapses occur after recovery from generalized miliary tuberculosis but the exact mechanism has not yet been demonstrated in many cases. It is possible that exacerbation in some cases may be due not to a reactivation of the miliary lesions but rather to a renewed softening and sloughing of the necrotic lesion in the lung or elsewhere which was the original source of the dissemination through the blood stream. If generalized infection is not diagnosed early and original treatment is not so effective, it may be expected that the residual lesions in various tissues of the body will have gone on to necrosis before subsiding and that bacteria may survive in these numerous foci for long periods of time. There is good evidence, for instance, to indicate that relapses of tuberculous meningitis after treatment may be due to such latent lesions remaining in the cortex of the brain.<sup>16</sup> These peculiarities of the pathology of tuberculosis have been repeatedly stressed by Medlar and are major considerations, aside from the natural resistance of the host and the antibacterial effects of the drugs. Obviously, therefore, each case must be judged according to an estimate of all these factors, realizing that the clinician is handicapped by many limitations of our knowledge. In practical terms one must consider not only the immediate response to treatment but also the probable ultimate behavior of the lesions and the probable requirements in terms of prolonged chemotherapy, surgical treatment and rest treatment. At best this is difficult and in recently developed cases a period of observation of at least a few months may be necessary before the long term prognosis can be estimated.

The variety of regimens of combined chemotherapy, that is, two or more drugs administered simultaneously, is great and may be expected to increase. A number of these have received broad and intensive study under the auspices of the United States Veterans Administration, Army and Navy Hospitals, the United States Public Health Service, and the

British Research Council. These agencies have made unique contributions which assuredly will be of permanent value in this field. The complexities are great, long periods of study are required, and it may be said that our present knowledge in many respects is only tentative. To illustrate the development of the regimens, it has been learned that the toxicity and disagreeable side effects of streptomycin can be avoided or minimized by limiting the dose to one gram daily or, preferably, to one or two grams every two or three days. Such low dosage, particularly in very active cases of tuberculosis may detract from the desired therapeutic effect but this objection is overcome and the effect is enhanced by the addition, for instance, of para-aminosalicylic acid in doses of 12 to 15 grams daily. The other advantage of the combination is the delay of bacterial drug resistance. The delay usually lasts for at least four months and in some cases much longer, a quality which is essential in view of the stubbornness and duration of tuberculous disease. Other regimens include isoniazid-para-aminosalicylic acid, isoniazid-streptomycin, and isoniazid-streptomycin-para-aminosalicylic acid. Their relative merits are still under study but their therapeutic effects approach each other rather closely. With any tested combination it has been shown that, while drug resistance may be delayed, it cannot with assurance be prevented eventually. Realizing as we must, therefore, that late exacerbations of tuberculosis may occur after initial recovery, there are reasons for withholding for possible future needs one or more drugs to which the bacteria have not become resistant. Since the two most potent drugs are streptomycin and isoniazid, many feel that only one of these should be used during initial treatment in combination with a less effective drug such as para-aminosalicylic acid. Such consideration may have to be thrown to the winds when the severity of the disease is extreme. Thus, in cases of meningitis and generalized miliary tuberculosis there is no hesitation in administering 2 grams of streptomycin intramuscularly daily with large doses of isoniazid (8 to 10 mg. per kilo per day) by mouth. This regimen has proved superior to others although some physicians like to add para-aminosalicylic acid also. A regimen of these three drugs might be expected theoretically to be superior to combinations of only two and there is some evidence that drug resistance is longer delayed by such a triple regimen and that the therapeutic effect may be more certain.<sup>17</sup> This varies undoubtedly with the urgency of the case and probable needs in the remote future; further study is required. In any

event it has been found important to continue a selected regimen consistently and without interruption until symptoms have been controlled and then usually for a further period of many months during which it may be anticipated that the sustained antibacterial effects will permit the repair of local lesions to proceed without interruption. During this time it may be wise to reduce the dose or frequency of administration of streptomycin to lessen the risk of its toxicity; there need not be much apprehension about toxic effects from isoniazid. Except for a judgment based on the clinical features of the case, the character of the lesions and the general experience to date, there is no precise way of determining when healing is adequate and chemotherapy may be discontinued. A course of six to eight weeks has seemed to be sufficient in some pulmonary cases but this is exceptional and, as a rule, the course is calculated in terms of six to twelve months, often longer. In other cases, particularly the advanced cavitory cases, prompt relapses have occurred at the conclusion of courses of treatment lasting for a couple of years. In the case of meningitis there is satisfactory evidence to indicate the wisdom of continuing combined therapy for at least a year after clinical recovery and the restoration of the spinal fluid to normal. After surgical operations, such as the resection of pulmonary lesions, chemotherapy is usually continued for at least six months to help insure the healing of the operative defect and to control minor lesions which cannot be reached by operation.

It would be a great advantage, of course, if a single inexpensive drug could be administered by mouth producing effects equal to those of combined therapy. Deuschle and his associates<sup>18</sup> have demonstrated the merits of isoniazid for this purpose and believe it may be so employed in special circumstances. The results will vary undoubtedly according to the severity of the disease. In some instances the favorable clinical effects may continue after the bacteria become resistant to isoniazid, and this is also true of other drugs. On the other hand, studies by ourselves and others have revealed unpredictable disadvantages recognized in failures to clear the sputum of tubercle bacilli and a greater frequency of eventual clinical relapse.

The great advantages of chemotherapy have had the expected effects of renewing interest in the possibilities of home care and of reducing the period of disability. As a consequence, many hospital beds have been evacuated. Matters are confused because of the uncertain durability

of early symptomatic recovery, the temptation of the patient to gamble and return too soon to work, and the pressure to reduce the expense of hospital treatment. The soundness of this trend will be determined only by limited and carefully organized studies since in some localities the situation is almost chaotic and the expectation of obtaining reliable information is nil. The possibility of a patient's losing his chance of permanent recovery by hasty decisions and undue reliance on chemotherapy is becoming evident in some cases. There has also been some apprehension regarding an increased dissemination of the infection among the population by patients discharged from hospitals before their disease is arrested. During the early years of the last war many tuberculosis hospitals in England were evacuated and patients were sent home. Numbers of these patients experienced an aggravation of disease and died, but the more alarming phenomenon was a sharp rise in the incidence and fatalities of the disease among children,<sup>19</sup> obviously due to their infection through close contact. During the present trend away from hospitals and toward treatment in the home, office and clinic, such results have been observed only in isolated instances. In New York among children under five years of age, 30 deaths from tuberculosis of the meninges and central nervous system were reported in 1941, and 37 in 1942, while despite the increase of children in our population there were only 24 such deaths in 1951 and 25 in 1952.<sup>20</sup> This index of communication of the infection seems to show that the current trend has not had dire effects generally. However, this death rate is no longer as meaningful as it once was since some patients in 1951-52 recovered from meningitis under chemotherapy. On the contrary, there is an impression, because of the frequent effect of chemotherapy in reducing the output of sputum, that the mass of infection disseminated in the community is diminishing. However, expectoration will recur in many poorly treated and poorly healed cases; some patients are already returning to hospitals on this account. Therefore, criteria are needed for advising the discharge from hospitals of patients still requiring treatment. In the Chest Clinic of Bellevue Hospital a systematic study of this problem is being conducted and this includes a survey of the home conditions to which the patient must return. It seems wise for the great majority of patients with active disease to undergo an early period of treatment and observation in a hospital in order to initiate treatment on a sound and safe basis and to evaluate their future prospects. The long

term plan of treatment may then be foreseen; the patient may be informed accordingly and may receive the education which is such a necessary element of his recovery.

In summary, the current methods of treatment of tuberculosis are more certain in their early favorable effects than those which were previously available. Bacteriostasis is exerted more promptly in active tuberculosis by chemotherapy than by the rest cure alone and early regression of the lesion, particularly resolution of inflammatory exudate, is accelerated impressively. The essential mechanisms of healing are not altered by chemotherapy and in no case can it be assumed that all, if any, of the lesions are sterilized. When tissue destruction has been extensive such healing is very undependable, and surgical treatment is often advisable. The field of surgical treatment has been widened since the introduction of chemotherapy and its effectiveness has been greatly improved. The selection of chemotherapeutic agents and regimens varies according to the site of the lesion and its physical character, the acuteness of the disease and the natural resistance of the patient. While permanent recovery is now more assured in many cases, the period of time required for initial treatment may not be greatly reduced. The trend away from hospital treatment is premature in many cases although treatment in the clinic and at home has a greater place than previously. The incidence of relapses is influenced, not only by medical treatment, but also by the understanding and cooperation of the patient and the circumstances which permit him to follow sound advice. The key to successful treatment is still early diagnosis and prompt action. There is ample room for improvement of methods of treatment and great need of further research in tuberculosis.

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